MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 20, 2001

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SUBJECT: Epidemiologic evidence of DHEA in the etiology of neoplasia
PID#: D000665

SUMMARY

We are not aware of any published epidemiologic studies that examine the cancer risk associated with exogenous dehydroepiandrosterone (DHEA) administration. However, one case-report was found to describe the medical condition of a patient with advanced prostate cancer after receiving DHEA. The cancer condition worsened after receiving DHEA, but when the patient stopped taking DHEA, the cancer regressed. Since the discontinuation of DHEA was accompanied by the initiation of estrogen therapy, the association of exogenous use of DHEA with the cancer progression is unclear.

In general the epidemiologic studies reviewed in this report have many limitations. Temporal precedence bias, small size, inability to control for confounding variables, and the method of DHEA measurement

are among the most common limitations of studies reviewed in this report. No meaningful conclusion about the association of exogenously administered DHEA and cancer risk can be made based on these epidemiologic studies of endogenous levels of DHEA.

INTRODUCTION

This consult follows Dr. Brinker's comprehensive report on the relationship of endogenous sex hormones and etiology of cancer dated January 4, 2000. The purpose of this consult is to review the literature again to identify any reports on exogenous use of DHEA and cancer risk.

In general, the epidemiological data addressing the association of endogeneous DHEA with cancer are very limited and the results are conflicting. The studies varied in study design and size, method of DHEA assessment, stage of cancer and ability to control for confounding variables. The study designs are either prevalence case-control or nested case-control studies. In general, the temporal association between DHEA levels and cancer cannot be established in prevalence case-control studies. In these studies, one cannot determine whether the change in DHEA level is caused by the cancer or whether any change in DHEA level is a predisposing factor for cancer. The size of the studies is often very small,so that, adjustment for confounding variables (even if they were collected) is not possible. In most studies reviewed, some of the important confounding variables were controlled by conducting a matched design followed by matched analysis.

In recent years, DHEA can be found at local health food stores, supermarkets, pharmacies, and Web pages from many companies, and is advertised as an antiaging agent. Therefore, any recent study of DHEA and cancer should consider both the use of DHEA as a dietory supplement and the level of endogenous DHEA. None of the recent studies ascertained any information on the exogenous use of DHEA. The method of measuring DHEA is also crucial and often is far from perfect in these studies. DHEA levels in serum change by diurnal and menstrual cycles. Thus any studies which examine DHEA should consider these cyclic sources of variability in their design.

We found one case-report study from the literature in which the author suggested that the administration of DHEA to patients with prostate cancer should be done with caution.

METHOD

We conducted a literature search by using the National Library of Medicine's PubMed search engine to identify epidemiological studies. We used *neoplasia* and *DHEA* to identify the studies. For the purpose of this report, we selected those studies which were not reported by Dr. Brinker previously.

STUDY SUMMARIES

Prostate Cancer:

Stahl et al (1992) conducted a prevalence case-control study to compare the DHEA levels in 19 prostate cancer patients with the DHEA levels in 23 age-matched controls. The DHEA level was assayed by RIA kits. They found that the levels of both DHEA and DHEAS (DHEA-sulfate) were significantly lower in prostate cancer patients than the control group. This study lacked any information on the quality of DHEA samples.

Comstock et al (1993) conducted a nested case-control study within a cohort of volunteers who participated in a [ ] Blood Bank study. From August to November 1974, 25,620 volunteers donated blood to study serum factor precursors of cancer. Comstock et al compared the DHEA/DHEAS level of 81 prostate cancer patients with 81 age-sex-race matched controls. All the cancer patients were diagnosed for the first time between 1974 and 1987. All blood specimens were frozen after donation and rethawed before reading. The serum samples of cases and their controls were assayed on the same day. DHEA/DHEAS levels were assayed by using radioimmunoassay (RIA) kits from Wein Laboratory. Although not statistically significant, this study showed that both DHEA and DHEAS levels were lower in prostate cancer patients than their control group. The authors noted no dose-response association with either DHEA or DHEAS. One potential limitation of this study is

temporal precedence bias. The possibility of this bias cannot be ruled out, since the latency of prostate cancer is long and the cancer patients could have had cancer at the time of blood donation.

Jones et al (1997) published a case report in which a patient with advanced prostate cancer was treated with DHEA. The administration of DHEA flared up his cancer while it reduced some of his symptoms. Upon the discontinuation of DHEA, the size and firmness of the prostate diminished, and the level of prostate-specific antigen (PSA) and testosterone decreased. Since the discontinuation of DHEA was followed by the initiation of estrogen therapy, it is not clear whether the improvement of his cancer was due to estrogen therapy or due to the discontinuation of DHEA. It is noteworthy that the patient was previously unresponsive to hormonal therapy, and whether the DHEA treatment had any impact on his conversion to being responsive to estrogen therapy is an interesting question.

Ovarian cancer

Helzlsouer et al (1995) conducted a nested case-control study within the [ ] blood blank study. They identified 31 newly diagnosed ovarian cancers between 1975 and 1989. For these cases, 62 controls were matched on age, menopausal status, and for premenopausal women, the number of days from the beginning of the last menstrual period. Serum samples were frozen at –70° C after donation and thawed right before preparing the aliquots for this study. The DHEA/DHEAS levels were assayed by using RIA kits and performed for each case and matched control set at the same day. The investigators showed that the levels of DHEA/DHEAS in serum were much higher in cases than controls. There could have been a temporal precedence bias in this study since the cases were identified within a year of blood donation. Whether some women had cancer at the time of blood donation is unknown. Weight, a known risk factor for ovarian cancer, was not collected, so the study could not control for its effect.

Breast cancer:

Zumoff et al (1981) conducted a prevalence case-control study, in which the 24-hr mean levels of

serum dehydroisoandrosterone (DHA) level and dehydroisoandrosterone sulfate (DHAS) of 11 women with primary operable breast cancer were compared with 37 healthy women. The DHA level was assayed by the radioimmunoassay technique as described by Rosenfeld and the DHAS was assayed by radioimmnoassay as described by Nieschlag. The study showed that postmenopausal breast cancer patients had higher DHA and DHAS plasma levels than the healthy women, while the premenopausal breast cancer patients had lowered DHA and DHAS than controls.

Solid tumors:

Lissoni et al(1998) conducted a prevalence case-control study to examine the association of DHEAS with stage of cancer. The study consisted of 70 patients with solid tumors and 100 age-sex-matched healthy controls. The histologic types of cancer were: gastrointestinal tract tumors:28; breast cancer: 24; non-small cell lung cancer: 18. There were 28 patients without and 42 patients with distant metastases. Blood sera were collected in the morning after an overnight fast, and DHEAS was assayed by RIA method using commercially available kits. The result of this study showed that irrespective of tumor histologic types, the serum level of DHEAS was similar between early cancer patients and the control group. Advanced cancer patients had much lower DHEAS levels than controls.

DISCUSSION

DHEA and DHEA-Sulfate are major adrenal secretory products in humans. They possess androgenic activity as they are metabolized to steroids such as testosterone. Thus, the association of testosterone and estrogen on the risk of breast cancer and prostate cancer can shed some light on the association of DHEA and neoplasia. While the evidence for an association between testosterone and the risk of prostate cancer is still conflicting, there is substantial evidence of an association between estrogen and breast cancer.

There are epidemiologoic studies which directly examined the association between endogenous DHEA and cancer risk; however, the epidemiologic evidence for an association is not consistent. For prostate

cancer, two epidemiologic studies [Stahl (1992) and Comstock (1993)] showed that cancer patients had lower DHEA levels than their non-cancer counterparts. Based on these studies, one might expect that DHEA therapy may improve the prostate cancer, however, the result from the case-report [Jones(1997)] suggests that the use of exogenous DHEA may worsen prostate cancer.

For ovarian cancer, compared to prostate cancer, a different result is suggested for the association of endogenous DHEA and cancer risk. The serum DHEA level was found to be higher in ovarian cancer patients than the control counterparts [Helzlsouer (1995)]. The association of DHEA and breast cancer could be different in pre- and post-menopausal women. In postmenopausal women, a positive association between DHEA level and breast cancer was reported by Cauley(1999) and Zumoff (1998) studies. The latter study showed that in premenopausal women, the level of endogenous DHEA was lower in breast cancer patients than the healthy controls.

In general the epidemiologic studies reviewed in this report have many limitations. Temporal precedence bias, small size, inability to control for confounding variables, and the method of DHEA measurement are among the most common limitations of studies reviewed in this report. No meaningful conclusion about the association of exogenously administered DHEA and cancer risk can be made based on these epidemiologic studies of endogenous levels of DHEA.

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